0022-5282/89/2907-0948$02.00/0
THE JOURNAL OF TRAUMA
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Vol. 29, No. 7
Printed in U.S.A.

Relationship of Transfusion and Infection in a Burn Population

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The relationship between the number of red blood cell transfusions and major infectious complications was evaluated in 594 thermal injury patients admitted between 1982 and 1986 who had burns over 10% or more of total body surface area and survived more than 10 days. The mean age of this group was 32.9 years, with a mean burn size of 36% of total body surface area; 83% were male. Of the 594 patients, 23.7% died and 38.7% had documented inhalation injury. The mean number of red blood cell transfusions received was 19.7, with a range of 0 to 201. Two hundred fourteen patients (36%) had major infectious complications, defined as pneumonia or invasive burn wound infection.

A cross-tabulation of predicted mortality, number of transfusions, and infectious complications revealed a significant positive correlation between transfusion number and infectious complications in patients with predicted mortalities between 10 and 70%. Per cent total burn, patient age, presence of inhalation injury, and number of transfusions were identified by discriminant function analysis as significant variables ($p < 0.05$) in discriminating between patients with and without infections (85% accuracy). Logistic regression analysis confirmed the above findings, showing a relationship between the number of transfusions received and infectious morbidity which was independent of age or burn size, but no significant relationship between number of transfusions and mortality.

A relationship between blood transfusions and perioperative infectious complications has recently been described (1). The transfusion of red blood cells before organ transplantation has been used to induce immunosuppression, thereby decreasing the frequency and severity of allograft rejection (2–6). The suppression of immunity associated with thermal injury contributes to the development of postburn infectious complications. The extent of the body surface burned, the patient's age, and the presence of inhalation injury all contribute to the increased incidence of infection in this population (7). We have evaluated the occurrence of major infectious complications in a population of burned patients to assess the effect of transfusion therapy on the incidence of infection in such patients.

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The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Presented at the 48th Annual Session of the American Association for the Surgery of Trauma, Newport Beach, California, October 6–8, 1988.

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MATERIALS AND METHODS

A retrospective analysis of the charts of all thermally injured patients admitted to the Institute of Surgical Research from January 1982 to December 1986 was performed. Inclusion criteria for entrance into this study were: 1) flame or scald burns involving more than 10% of the total body surface area and 2) survival for more than 10 days following injury. Patients with electrical or chemical injury were excluded from analysis.

For each patient, age, sex, total extent of burn (% BSA), extent of full-thickness burn, the presence of inhalation injury, major infectious complications, the number of red blood cell transfusions received during hospitalization, and ultimate outcome were recorded. Inhalation injury was diagnosed by bronchoscopic examination or ^{133}Xenon ventilation-perfusion lung scan. Major infectious complications were defined as pneumonia or invasive burn wound infection. Diagnoses of pneumonia were based upon findings of an elevated sputum leukocytosis, positive sputum culture, appropriate clinical signs, and an infiltrate evident on chest roentgenogram. Burn wound infection was defined as the presence of microorganisms (bacteria, fungi, or viruses) in viable tissue on histologic examination of a burn wound biopsy.

Cross-tabulation, log-linear analysis, discriminant function analysis, and multiple logistic regression were used in conjunction with three-dimensional graphics to examine the relationship of severity of injury, number of transfusions, and the presence or absence of inhalation injury to both mortality and infectious morbidity in the study population.

RESULTS

Charts of 986 thermally injured patients admitted to the Institute of Surgical Research between January 1982 and December 1986 were reviewed. Patients with electrical or chemical injury were excluded. Five hundred ninety-four patients met the entrance criteria of greater than a 10% total body surface area burn and survival for more than 10 days following injury.

The mean age of the 594 patients was 32.9 years (range, 2-93). Eighty-three per cent were male (497) and 17% female (97). The mean burn size was 36%, with a mean extent of full-thickness injury of 18%. Inhalation injury was documented in 230 patients (38%); 23.7% of the patients died (n = 141). The mean number of red cell transfusions received was 19.7 units, with a range of 0–201. Burn wound infection or pneumonia was documented in 36% of the patients (n = 214). These data are summarized in Table I.

Logistic regression analysis was performed to identify the relationship between the number of transfusions received and the presence or absence of infection and ultimate outcome. No relationship between the number of transfusions and mortality could be identified. The total extent of burn, a cube function of age, and the presence of inhalation injury were identified as significant variables in discriminating between patients who survived and those who did not. The percentage of the total body surface area burned, a square function of age, the number of transfusions received, and the presence of inhalation injury were identified as significant variables in discriminating between patients with and without infection. This analysis demonstrates a relationship between the number of transfusions received and infectious morbidity which is independent of age, extent of burn, or the presence of inhalation injury.

The data were cross-tabulated with segregation based upon predicted mortality and the number of transfusions received as related to infectious complications and actual outcome. This was done to identify the patients in whom the number of transfusions had the greatest effect on infectious morbidity. Predicted mortality, used as an index of severity of injury, was based upon a multiple logistic analysis of the relationship of burn size and age to the occurrence of death in all burned patients admitted to this Institute between 1980 and 1986. Since patients who did not survive for 10 days were excluded from analysis in this review, the predicted and actual outcomes differed slightly (Table II). Table III documents the increase in the rate of infection as the probability of death increased. There was a 13% incidence of infection in patients with a 0 to 20% probability of dying, and this increased to a 97% incidence of infection in the patients with greater than an 80% probability of dying. The distribution of the number of transfusions received compared to the probability of death is depicted in Table IV. There was a progressive increase in the transfusion requirements as probability of death increased up to 80%. Patients with greater than an 80% probability of dying received fewer transfusions and also spent fewer days in the hospital, presumably because of their higher early death rate. As expected, age, total extent of burn, and extent of full-thickness burn all increased as the probability of death increased (Table V).

A three-dimensional plot of number of transfusions received, probability of death, and actual outcome is depicted in Figure 1. This "tent" diagram is useful in

TABLE I

	x ± S.D.	Range
Age (yrs)	32.9 ± 21.3	2-93
TBSB (%)	35.9 ± 20.7	0-97
% 3°	17.9 ± 20.9	0-97
Transfusion	19.7 ± 27.3	0-201
Inhalation injury	38.7%	230
Infection	36.0%	214
Sex	83.7% male/16.3% female	
Outcome	23.7% mortality	

TABLE II

n	Predicted Mortality (%)		Actual Mortality (Mean)
	Range	Mean	
374	0–20	0.05	0.045
61	21–40	0.28	0.21
42	41–60	0.49	0.33
49	61–80	0.68	0.69
68	81–100	0.90	0.92

TABLE III

Predicted Mortality (%)	Incidence of Infection
0–20	13.4%
21–40	45.9%
41–60	69.0%
61–80	83.2%
81–100	97.1%

TABLE IV

Predicted Mortality (%)	Number of Transfusions (units)
0–20	10.9 ± 16.7
21–40	25.4 ± 23.2
41–60	36.9 ± 32.5
61–80	47.8 ± 43.0
>80	32.1 ± 34.6

TABLE V

Predicted Mortality (%)	Age (yrs)	TBSB %	% 3°
0–20	25.2 ± 15.4	25.3 ± 10.5	9.1 ± 10.9
21–40	40.2 ± 20.2	41.9 ± 13.4	20.2 ± 14.9
41–60	41.8 ± 27.2	45.7 ± 19.2	24.6 ± 20.4
61–80	49.9 ± 23.4	51.0 ± 19.6	30.9 ± 20.8
>80	51.3 ± 22.4	71.6 ± 18.7	50.6 ± 27.9

demonstrating the lack of relationship between number of transfusions received, probability of death, and actual outcome. As expected, patients receiving few transfusions and having a low probability of death had a low actual mortality rate. As the number of transfusions increased in this low probability group, mortality increased slightly but not significantly. Figure 2 depicts a three-dimensional plot of number of transfusions received, probability of death, and infection rate. In contrast to Figure 1, there was a significant relationship between number of transfusions received and infection rate in the patients with lower probabilities of death. As expected, as the probability of death increased, so did the infection rate, interacting with the number of transfusions received.

DISCUSSION

This study demonstrates that the number of red blood cell transfusions and severity of injury, as indexed by the likelihood of death based on age and burn size, were significantly and independently correlated with the risk of serious infection following thermal injury in these patients. This relationship may only mean that more frequent transfusion identifies the patients at any particular level of severity of injury who experienced more severe complications; such patients would be expected to experience infection more frequently than those whose courses were not complicated. The data may, instead, depict the consequences of a specific depression of resistance to infection caused by transfusion. The observations are equally compatible with either interpretation.

The concept of blood transfusion-induced immunosuppression evolved from a large number of retrospective human studies in the early 1970's which demonstrated that pretransplant transfusion decreased the frequency and severity of rejection of transplanted solid organs (2–6). Subsequently, a randomized study showed similar results in a series of patients undergoing cadaver renal transplant (8).

Following recognition of blood transfusion as an immunosuppressive therapy in transplant patients, allogeneic blood transfusions were found to enhance tumor growth in animal models. This effect was specific to allogeneic transfusions and was not seen with syngeneic transfusions (9, 10). The effects of perioperative transfusion on outcome in patients with carcinoma of the colon, rectum, lung, and breast have been reviewed (1). Nine of 13 such reports have described increased rates of tumor recurrence and decreased long-term survival in

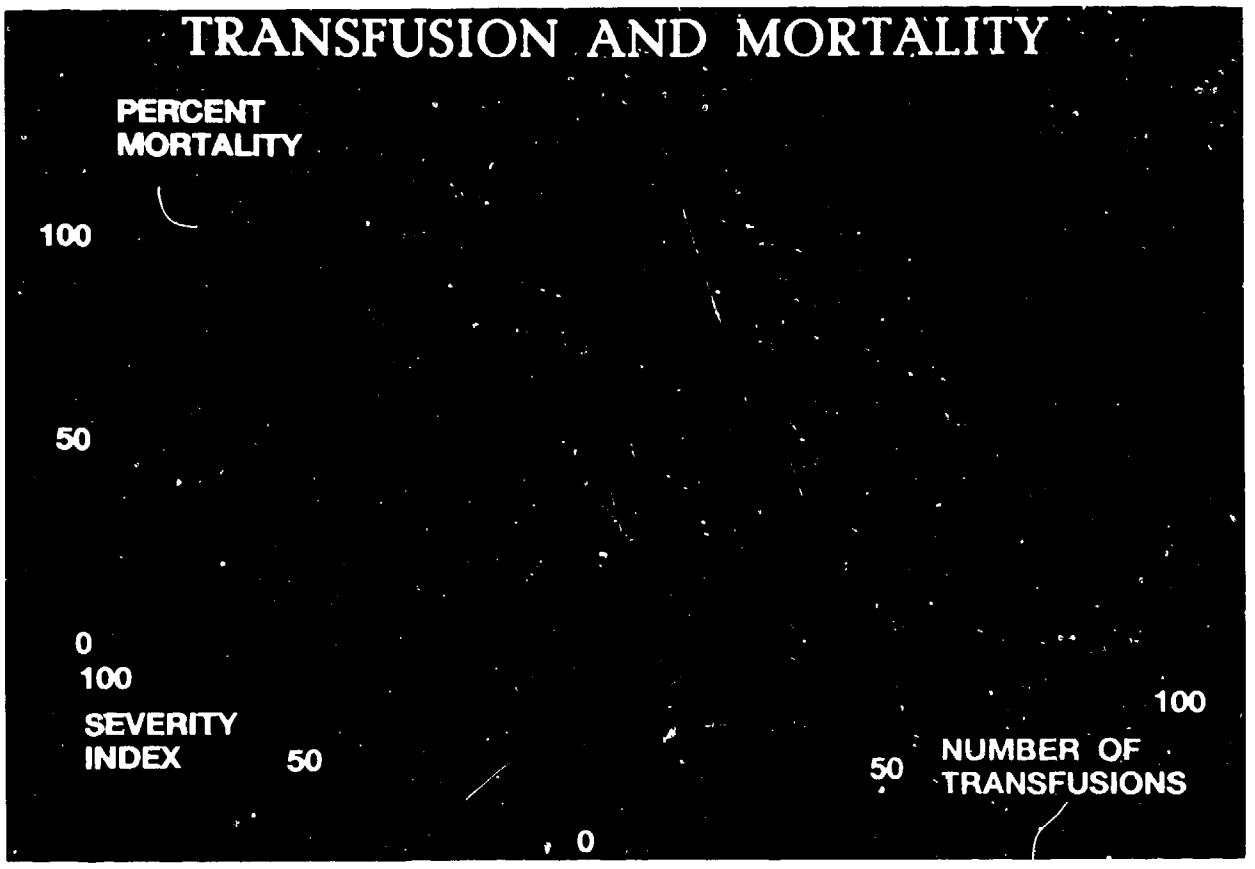

FIG. 1. Number of transfusions received, predicted mortality, and actual outcome for the 594 patients are plotted in a three-dimensional graph. Transfusion number does not appear to alter actual mortality. Patients receiving few transfusions with a low predicted mortality had a low actual mortality rate. As the number of transfusions increased, actual mortality increased only slightly. For any given transfusion number, actual mortality appeared not to be correlated.

FIG. 2. Number of transfusions received, predicted mortality, and infection rate for the 594 patients are plotted on a three-dimensional graph. For any given predicted mortality up to approximately 70%, the number of transfusions received was positively correlated with the infection rate.

the patients to whom perioperative transfusions were given. In many of the studies, multivariate analysis indicated that the effect could not be related to confounding variables such as tumor stage, or the length and difficulty of the operative procedure.

While the specific immune mechanism which leads to improved allograft survival after transfusion is not known, a variety of mechanisms have been proposed. Most of the relevant studies have been conducted on patients with renal failure. Following transfusion of packed red blood cells in dialysis patients, inhibition of lymphocyte response to mitogens and antigens has been noted, as well as increased T-lymphocyte suppressor cell activity and a decrease in the T-cell helper/suppressor cell ratio (11, 12, 14, 15). Decreased natural killer cell activity has also been reported following transfusion in hemophiliacs (15). In a series of thoracic surgery patients, perioperative transfusions have been associated with a depressed lymphocyte response to PHA, pokeweed mitogen, and concanavalin A which lasted up to 4 weeks (16). Prolonged depression of peripheral T-lymphocyte function has also been noted in patients with Crohn's disease who were transfused perioperatively (17).

A relationship between transfusion and perioperative infection has been noted in several patient populations. Tartter reviewed the charts of 169 patients with Crohn's disease who underwent bowel resection for complications of their disease. Postoperative septic complications occurred in 26 of the 169 patients and were threefold more common in the patients who were transfused perioperatively (18). The same investigator reviewed the charts of 168 patients undergoing elective operation for colorectal cancer and again demonstrated a relationship between perioperative transfusion and postoperative septic complications (19). In both studies, multivariate analysis demonstrated that blood transfusions were associated with an increase in infectious complications independent of other known predisposing factors. In a multicenter study, Nichols reported that the risk of infection after penetrating abdominal trauma was clearly increased when the patients required perioperative transfusions. This relationship could not be attributed to other predisposing factors such as preadmission shock (20).

In this retrospective review of 594 thermally injured patients, as in the cited studies, blood transfusions were found to be associated with an increase in infectious complications even when other independent and known predisposing factors were controlled. The relationship between the number of transfusions received and infectious morbidity was independent of age, presence of inhalation injury, or burn size. However, no relationship could be found between the number of transfusions and

ultimate outcome in these patients. Since infection is the leading cause of death in burned patients, any factor increasing the incidence of infection should affect mortality. Figure 2 best depicts this relationship in which significant positive correlation between transfusion number and infectious complications was evident in patients with predicted mortalities between 0 and 70%. It should be noted that this analysis indicates that the number of blood transfusions correlated over its entire range with the likelihood of occurrence of major infectious complications. Such data do not, however, prove a direct causal relationship.

Support for the possibility of a causal relationship can be found in animal studies. Waymack demonstrated in Lewis rats which underwent 30% total body surface burns and were subsequently infected with *Pseudomonas* (strain 1244), that allogeneic transfusions significantly decreased overall survival and mean survival time compared to animals which received syngeneic transfusions or saline (21, 22).

It is speculated that the immunomodulating effects of blood transfusions are related to the HLA antigens on leukocytes and platelets which accompany the transfused red blood cells (23). The washing and centrifugation process for the preparation of frozen blood markedly reduces the HLA antigen content. Patients who receive transfusions of frozen blood have a lower incidence of induction of anti-HLA antibodies. Pure red-cell preparations, however, may not be totally free of immunomodulating effects since it has been shown that phagocytosis of red blood cells by macrophages results in a decreased reactivity of bystander lymphocytes. If it is assumed that leukocytes and platelets are the major sources of factors mediating immunosuppression following red blood cell transfusions, a method for depleting the blood of these elements could be beneficial. Several methods for depleting red cell transfusions of platelets and white blood cells are currently available, including filter systems and pheresis.

The use of transfusion is not optional in burned patients, nor are the procedures and complications which compel more frequent transfusion in some of these patients avoidable. This study may indicate the presence of transfusion-specific immunosuppression; alternatively, it may indicate only that patients who sustain complications sustain greater risk of infection; or it may equally well indicate both. The use of blood transfusion, like the use of any other modality of treatment, carries with it both benefit and risk; these must be carefully weighed and balanced whenever any treatment is used. The present study suggests that it is at least possible that some additional weight should be added to the risk side of this balance.

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DISCUSSION

DR. DAVID M. HEIMBACH (Seattle): It is a privilege to discuss this well done paper. The people at San Antonio have once again taken advantage of their very large experience with burned patients, this time from the years 1982 through 1986.

They studied all patients with burns greater than 10% and they found a remarkable thing that I think we should all keep in mind, that these patients needed on the average almost 20 units of blood throughout their hospital stay. Why do burned patients need so much blood? There is a lot known about blood dynamics in burned patients. For example, we know that the half-life of red blood cells in burned patients is decreased by about half, related to a circulating factor, since when the cells are removed from the burned patients and transfused into normal individuals, the half-life comes back to normal. By the same token, if you take normal blood cells and put them into a burned patient, their half-life goes down to approximately 50%.

We also know that burned patients who are critically ill for a long period of time receive a lot of blood tests. In our burn unit as much as 300 to 400 cc per week is removed through clinical and research activities. We also know that a normal individual takes probably 10 to 14 days at least to resume that amount of blood by erythropoeisis, so progressive anemia is inevitable.

Finally, the burned patient has a large open wound. In many places these wounds are excised and grafted, and we know that a major excision on a grafting procedure may use up as much as a whole blood volume. In addition daily wound debridement causes a substantial amount of blood loss in small quantities every day.

As an example of progressive anemia we had a 35-year-old patient unfortunate enough to be a Jehovah's Witness who suffered a 40% scald burn which was all partial thickness. He, during the course of his 21-day life in the hospital, did not undergo massive blood loss. He underwent the micro laboratory techniques we use for our pediatric patients. He had no oozing from his wounds, but by the 24th postburn day, his hematocrit was 5%, at which point he went into florid forward cardiac failure and he died.

It is clear that blood transfusions are filled with many hazards, besides the transmission of disease. Doctor Graves has reviewed much of the data regarding transfusion and the immune system but just again to say that in chronic renal failure we know that T cell suppressor/helper ratios are altered, that the lymphocyte response to mitogens is seriously impaired and that chemotaxis and chemiluminescence are decreased. It is of interest that these very same cellular defects take place in burned patients whether or not they have had any blood transfusions.

We also know that these blood transfusions have been associated with infectious complications in Crohn's disease, and following cancer operations both in terms of tumor recurrence and infections. Infectious complications increase with penetrating trauma to the abdomen when transfusions are needed and in rats with blood transfusions and burns infected with *Pseudomonas*. But over and above the association with transfusion, interestingly, the burned patient already has a substantial immunosuppression probably related to circulating features. We know that he has decreased killer cells and decreased response of white cells in virtually every one of their immune functions, which seems to occur with or without transfusions.

Furthermore, Doctor Glenn Warden in some studies a few years ago demonstrated that excising and grafting large wounds essentially requiring an exchange tranfusion did *not* impair the immune response but actually improved the cellular response to stimuli as well as normalizing the ratio of helper cells to suppressor cells. So it may be that the features of the burn itself and the things that are circulating in the burn tissue may be even more important than the role of the transfusion in such a patient.

I would then ask the authors just two questions. I have no real quibble with their data.

Have you actually done or are you planning to do any immune function measurements in the patients as you give them transfusions? I think this would be a golden opportunity and, since you are well set up to do that, I would wonder if you have, and second, do you have enough courage of your convictions at this point that you are, in fact, using washed cells rather than regular blood transfusions?

Thank you. [Applause]

DR. DAVID LIVINGSTON (Newark, New Jersey): While I was at the University of Louisville, they were looking into this question with regard to cytomegalovirus infection in predominantly nonthermally injured patients. It appears from the data that it didn't really matter whether you received many transfusions or a few transfusions but if you got cytomegalovirus infection you had a longer hospital course with a higher infectious morbidity. CMV in and of itself is immunosuppressive and the question I pose to the authors is: have they looked at any transmittal virus such as CMV, Epstein-Barr, etc., as they impact on infectious morbidity in their patients?

DR. ROBERT F. WILSON (Detroit, Michigan): We have had some interest in the effect of massive transfusions on infection rates. We have been impressed that it is how many units of blood the patients are given in any one 24-hour period that is important. The total amount they receive throughout their hospitalization is less significant. I wonder if the authors have any data which would allow them to correlate the infection rates with the number of blood transfusions that their patients received during the first 24 hours.

We have also noted that individuals who have enough transfusions and/or shock to develop abnormalities of their PT or PTT seem to have a particularly increased risk of infection. These patients frequently also have significantly reduced plasma levels of antithrombin, fibronectin, and prekallikrein, which seem to have a very significant effect on the infection rate. I wonder if they have any data on coagulation studies in their patients and if there were any relationship between the infection rate and the extent of these coagulation changes.

Thank you.

DR. CHARLES RICE (Seattle, Washington): I would like to congratulate the authors on an excellent paper and presentation.

A couple of questions. One is, what was the indication for red cells? In other words, was there some absolute level of hematocrit that was always sought?

Second, do you have any data on the use of other blood products such as fresh frozen plasma or platelets and were those independently looked at?

DR. ERWIN HIRSCH (Boston): About a year ago we looked at the age of the blood transfused to cardiothoracic patients at the West Roxbury Veterans Administration Hospital and multiply transfused trauma patients at the Boston City Hospital. The mean age of the blood was 41 days; such units usually have around 22–23% of nonviable cells.

Do the authors know how old was the blood transfused in San Antonio? Perhaps the nonviable cells transfused may be responsible for the complication described.

DR. MARK MALANGONI (Louisville, Kentucky): I would like to congratulate you on an excellent presentation and I wish to comment on some things that I think are important.

In the penetrating abdominal trauma studies that looked at transfusion as a marker of infection, you must remember that transfusion tended to be significant only after shock dropped out as a variable. Transfusion is thought by many people to be a more sensitive indicator of the degree of shock in the patient with penetrating abdominal trauma. It may be that your patients probably got most of their blood replacements surrounding the time of excision and grafting or some other acute event, so that your postulate that transfusion is a positive indicator

of the risk of infection rather than an absolute cause for the infection may turn out to be very important.

Based on that hypothesis, I would ask you if you have quantified any minor incompatibility reactions or major incompatibility reactions in your patients and tried to correlate those with their degree of infection?

DR. GEORGE WATKINS (Easton, Pennsylvania): It is important to point out and hope the authors point out that this study is not an indictment of transfusion per se. One of the tendencies of present day blood bankers would be that this paper is more evidence one "should not transfuse someone."

Those patients who died were, of course, terminated as far as the study. Those who survived were transfused more, had more infections, and were surviving longer. I do not know that this study would be an indictment of transfusion in spite of the increase in complications. The mortality in this series was at least the predicted probability or less. I suspect that the mortality is dropping constantly over time in the authors' center as it is in most.

Therefore, transfusion itself may in part produce a model that is more likely to be infected repetitively because the model is surviving but at risk for infection over a longer time. This view is diametrically opposite to one that the transfusion itself causes some sort of specific problem leading to more infections.

DR. THERESA GRAVES (Closing): Thank you, Doctor Heimbach, and fellow members for your comments and questions concerning this work.

To address Doctor Heimbach's discussion, immune function evaluations were not routinely performed during the course of this study period and were not included in this retrospective review. The efficacy of washed cells as a means of avoiding the immunosuppressive properties of transfusions has been raised. As a preliminary study this work has again suggested a relationship between immunosuppression and transfusions and as such supports the need for a prospective, randomized evaluation comparing washed or pheresed cells with standard red blood cell transfusions. Additionally, an evaluation of immune function would be concurrently analyzed.

Doctor Livingston has questioned the relationship between immunosuppression and cytomegalo- and Epstein-Barr virus infections. Blood transfusion transmission of viral infections was not evaluated in this group of patients. Presently, we routinely evaluate patients for HIV status.

The question of how many units of blood are administered over what period of time is raised by Doctor Wilson. Most of the blood transfusions administered at the Burn Unit are associated with excision and grafting procedures, episodes of hypotensive shock, or more chronically with the red cell loss from daily sampling. For the former, blood transfusions range from 5 to 12 units of blood over minutes to several hours. This study did not delineate individual episodes of transfusion, nor specify the chronologic relationship between transfusion and infectious complications. This would be necessary to support a causal relationship.

Collectively, there are several salient questions raised at this discussion that are pertinent but were not within the scope of this retrospective study, including the relationship of coagulation status (PT and PTT), transfusions, and infections, or the age of the blood products being transfused. Even more critical is the fresh frozen plasma and non-red-cell blood product transfusions which may affect immunomodulation, as Doctor Rice has implied.

Our review suggests that blood transfusions may alter a patient's incidence of infection, independent of the size of the burn wound, a known immunodepressor. Whether the transfusions alter burned patients' existing immunodepressed state is unknown. This review is incapable of indicating an absolute level of hematocrit, referring to Doctors Malangoni, Rice, and Watkins' questions and comments. Nor is it proposed as an indictment of blood transfusions. The successful treatment of burned patients is in part made possible by our ability to offer blood transfusions.

We have seen a changing attitude at the Burn Unit toward adequate baseline hematocrits, based on a patient's physiologic status, pre-existing medical conditions, and age, hematocrits in the upper 20's may be considered adequate. We remind surgeons to be aware of the benefits and potential immunomodulating consequences of transfusions.

I would like to thank the Association, members and guests for the privilege of presenting this paper.